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Chapter 3: Osteoporosis

INTRODUCTION

- *Osteoporosis* is a bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength predisposing to fracture.

CLINICAL PRESENTATION

- Many patients are unaware of osteoporosis and initially present after a fracture. Fractures may occur with bending, lifting, falling, or even without trauma.
- The most common fracture sites are the vertebrae, proximal femur, and distal radius (wrist/Colles fracture). Vertebral fractures may be asymptomatic or cause moderate to severe back pain radiating down a leg. Pain usually improves within 2–4 weeks, though residual back pain may persist. Multiple vertebral fractures can reduce height and cause spinal curvature (kyphosis or lordosis).
- Nonvertebral fractures typically cause severe pain, swelling, and decreased function at the site.
- Drug-induced osteoporosis can result from systemic corticosteroids, excessive thyroid hormone replacement, antiepileptics (eg, phenytoin, phenobarbital), depot medroxyprogesterone acetate, and other medications.

DIAGNOSIS

- The World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX) estimates 10-year fracture probability using the following factors: age, race/ethnicity, sex, prior fragility fracture, parental hip fracture, body mass index, glucocorticoid use, smoking, alcohol intake (≥3 drinks/day), rheumatoid arthritis, and select secondary causes. Femoral neck or total hip bone mineral density (BMD) can be included but is optional.
- FRAXPlus refines conventional FRAX estimates by adding: recency of osteoporotic fracture, higher oral glucocorticoid exposure (>7.5 mg/day), an updated trabecular bone score, number of falls in the past year, duration of type 2 diabetes, lumbar spine BMD, and hip axis length (above average). Tools like the Garvan fracture risk calculator also include fall history, but the risk models are based on smaller cohorts.
- Physical exam findings may include bone pain, kyphosis, and height loss (>1.5 in [3.8 cm]).
- Recommended laboratory tests include complete blood count, serum creatinine, calcium, phosphorus, electrolytes, alkaline phosphatase, albumin, thyroid-stimulating hormone, total testosterone (in men), 25-hydroxyvitamin D, and 24-hour urine calcium and phosphorus.
- Bone turnover markers—used in trials and sometimes in practice—help assess bone physiology, monitor treatment response, evaluate adherence, and guide decisions on restarting bisphosphonates after a drug holiday. The preferred formation marker is serum carboxyterminal propeptide of type-1 collagen, and the preferred resorption marker is serum C-terminal telopeptide type-1 collagen.
- Central (hip and spine) BMD measurement with dual-energy X-ray absorptiometry (DXA) is preferred for treatment decisions. Peripheral DXA or quantitative ultrasonography (forearm, heel, finger) is used only for screening and determining the need for further testing.
- A T-score compares a patient's BMD with that of a healthy young (20–29-year-old) white female reference population. It is not adjusted for age, sex, race, or ethnicity and represents the number of standard deviations from the reference mean.
- Osteoporosis is diagnosed by a low-trauma fracture or by femoral neck, total hip, or spine DXA using WHO T-score thresholds: normal if more than −1, low bone mass (osteopenia) −1 to −2.4, and osteoporosis if −2.5 or less.

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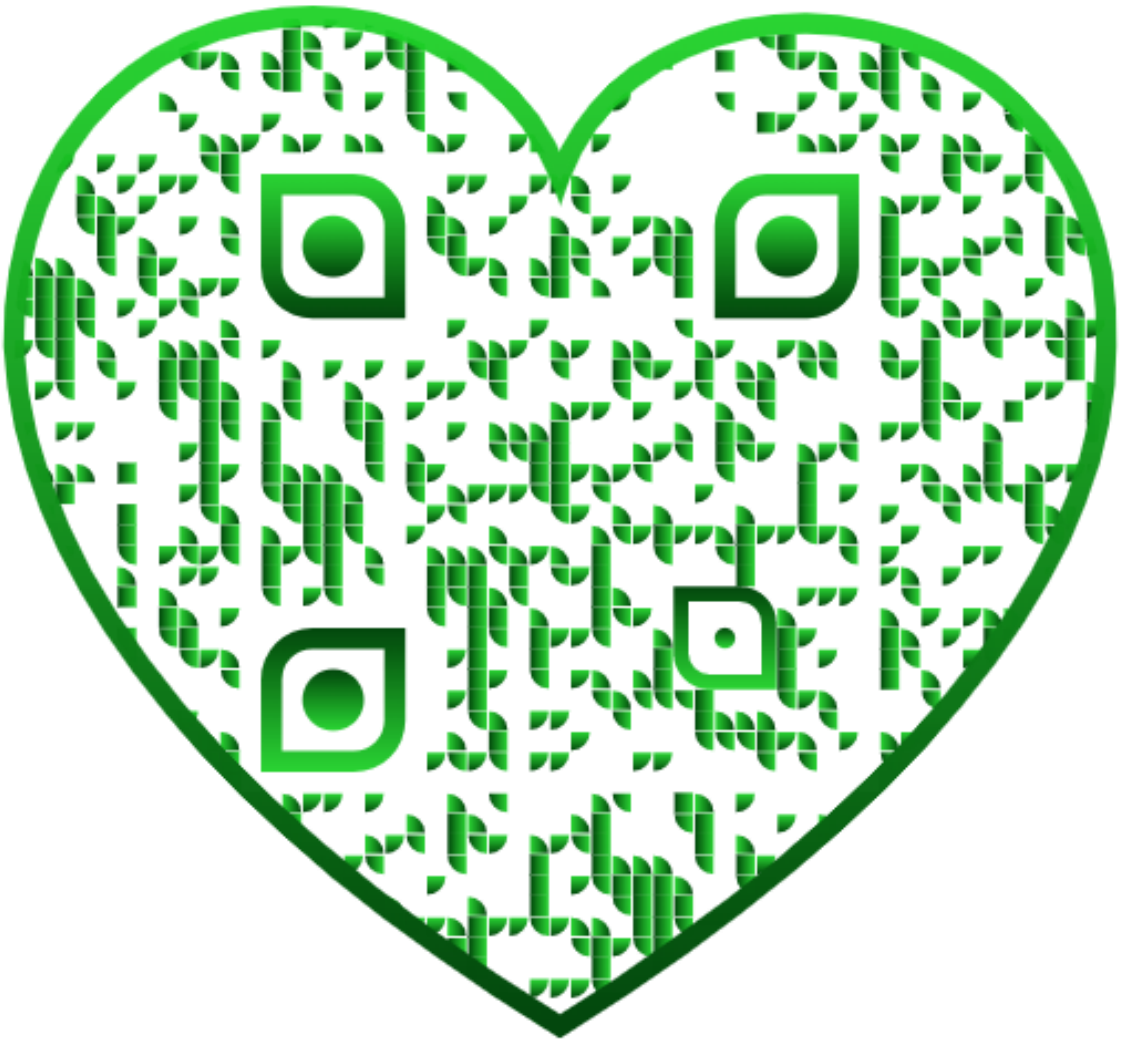

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TREATMENT

- Goals of Treatment: The primary goal of osteoporosis care is prevention. Optimizing peak bone mass in youth lowers future osteoporosis risk. Once low bone mass or osteoporosis develops, the aim is to maintain or improve bone mass and strength and prevent fractures. For patients with osteoporotic fractures, goals include reducing pain and deformity, improving function, lowering fall and fracture risk, and enhancing quality of life.
- **Figure 3-1** outlines a management algorithm for postmenopausal women and men aged 50 and older.

FIGURE 3-1

Algorithm for osteoporosis management in postmenopausal females and men aged 50 and older.

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; FRAX, World Health Organization Fracture Risk Assessment Tool. [a]Major clinical risk factors for fracture: current smoker, low body weight or body mass index, personal history of fracture as an adult (after age 50 years), history of osteoporosis/low-trauma fracture in a first-degree relative, excessive alcohol intake. [b]Bone-healthy lifestyle includes well-balanced diet with adequate calcium, vitamin D, and protein intakes; smoking cessation; limited alcohol intake; weight-bearing/resistance exercises; and fall prevention. [c]Dietary calcium preferred. If diet is inadequate, supplement as necessary. [d]Higher vitamin D doses might be needed to achieve 25-hydroxyvitamin D concentrations ≥30 ng/mL (mcg/L; 75 nmol/L). Vitamin D recommendations vary by organization. [e]High risk or very high risk depending on the number of fractures, fracture site, and other clinical risk factors. [f]For glucocorticoid-induced osteoporosis, see textbook Tables 117-9 and 117-10. [g]Bisphosphonates are lower in cost than denosumab and preferred in some guidelines, with some guidelines recommending oral bisphosphonates as first-line (alendronate, risedronate).

NONPHARMACOLOGIC THERAPY

- All individuals should have a balanced diet with adequate intake of **calcium** and **vitamin D** (**Table 3-1**). Obtaining daily calcium from food sources is preferred.

  ✓ To estimate elemental calcium in a serving, add a zero to the percent daily value on the food label. For example, an 8-oz (240 mL) serving of skim milk provides 30% of the daily value, or about 300 mg of calcium.

  ✓ For patients with low bone mass or osteoporosis, guidelines recommend vitamin D intake sufficient to maintain a 25-hydroxyvitamin D level of 30 ng/mL (75 nmol/L). To estimate vitamin D in food, multiply the percent daily value by 4; for example, 20% equals 80 units.
- Protein is essential for bone formation. The recommended dietary allowance is 0.8 g/kg/day, but older adults are often advised to consume 1–1.2 g/kg, and those who exercise regularly or have certain acute or chronic illnesses may need 1.2–1.7 g/kg/day.
- Alcohol should be limited to 1–2 drinks per day for women and 2–3 for men.
- Caffeine intake should ideally be two or fewer servings daily, as higher amounts are linked to increased calcium excretion, greater bone loss, and a modest rise in fracture risk.
- Smoking cessation helps optimize peak bone mass, slows bone loss, and lowers fracture risk.
- Weight-bearing aerobic and strengthening exercises help reduce falls and fractures by improving muscle strength, coordination, balance, and mobility. In older adults, such activity also increases bone strength. Moderate-intensity weight-bearing (eg, running, jumping) and resistance training (eg, weights, elastic bands) support bone health. Those at risk should exercise three to four times weekly for 30–40 minutes if able.
- Multifactorial fall-prevention programs can reduce falls, fractures, other injuries, and related hospital or nursing home admissions.

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TABLE 3-1

Calcium and Vitamin D Recommended Dietary Allowances (RDAs) and Tolerable Upper Intake Levels

Group and Ages	Elemental Calcium RDA (mg)	Calcium Tolerable Upper Intake Level (mg)	Vitamin D RDA (Units)[a]	Vitamin D Tolerable Upper Intake Level (Units)
Infants				
Birth–6 months	200[b]	1000	400[b]	1000
7–12 months	260[b]	1500	400[b]	1500
Children				
1–3 years	700	2500	600	2500
4–8 years	1000	2500	600	3000
9–18 years	1300	3000	600	4000
Adults				
19–50 years	1000	2500	600[b,c]	4000
51–70 years (men)	1000	2000	600[b,c]	4000
51–70 years (females)	1200	2000	600[b,c]	4000
>70 years	1200	2000	800[b,c]	4000

RDA, recommended dietary allowance.

[a]Some guidelines recommend intake to achieve a 25-hydroxyvitamin D concentration >30 ng/mL (mcg/L; 75 nmol/L), which is higher than the Institute of Medicine goal of >20 ng/mL (mcg/L; 50 nmol/L).

[b]Adequate intake (evidence insufficient to determine an RDA).

[c]Guidelines recommend 800–1000 units or 1000–2000 units for adults with osteoporosis.

PHARMACOLOGIC THERAPY

General Approach

- Because nonpharmacologic measures alone often cannot prevent or treat osteoporosis, medication is frequently required.
- All medications should be used alongside a bone-healthy lifestyle.

Antiresorptive Therapy

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Calcium Supplementation

- Calcium generally maintains or slightly increases BMD, though its effects are smaller than other medications. While data are insufficient to show that calcium and vitamin D supplements reduce fractures, supplementation is important for patients who cannot meet requirements through diet.
- Because calcium absorption decreases at higher doses, single doses no larger than 500–600 mg elemental calcium are recommended.
- **Calcium carbonate** (40% elemental calcium) is preferred for its high calcium content and low cost. Take with meals to enhance absorption in an acidic environment.
- **Calcium citrate** (21% calcium) absorbs independent of stomach acid and does not require meals; it may cause fewer gastrointestinal (GI) side effects.
- **Tricalcium phosphate** (38% calcium) may have limited absorption due to calcium-phosphate complexes but can be useful in patients with hypophosphatemia uncorrectable by diet.
- Constipation is the most common side effect and can be managed with increased water intake, fiber (separate from calcium), and exercise. Calcium carbonate may also cause gas or stomach upset. Kidney stones are rare.
- Calcium can reduce oral absorption of some medications, including iron, tetracyclines, quinolones, bisphosphonates, and thyroid supplements.

Vitamin D Supplementation

- **Vitamin D** supplementation of 700–800 IU/day significantly lowers hip and nonvertebral fracture risk, modestly increases BMD, and improves muscle strength and balance.
- Vitamin D can be taken alone or in combination products as D_3 (cholecalciferol) or D_2 (ergocalciferol). For insufficiency or deficiency, guidelines recommend 5000 IU daily for 8–12 weeks to reach a 25(OH) vitamin D level ≥30 ng/mL (75 nmol/L), followed by a maintenance dose of 1000–2000 IU daily. Vitamin D_3 is preferred.
- Recommended daily allowances (**Table 3-1**) should be met through diet and supplementation.
- With a half-life of ~30 days, vitamin D requires about 3 months of therapy to reach a new steady state, after which 25(OH) vitamin D levels should be rechecked to assess efficacy.
- Medications that increase vitamin D metabolism include rifampin, phenytoin, barbiturates, valproic acid, and carbamazepine. Vitamin D absorption may be reduced by cholestyramine, colestipol, orlistat, and mineral oil. Vitamin D can increase aluminum absorption, so aluminum-containing products should be avoided to prevent toxicity.

Bisphosphonates

- Bisphosphonates (**Table 3-2**) mimic pyrophosphate, an endogenous inhibitor of bone resorption, reducing osteoclast maturation, number, recruitment, adhesion, and lifespan. Their incorporation into bone gives bisphosphonates long half-lives of up to 10 years.
- They consistently increase BMD and reduce fracture risk, though fracture site reduction varies by agent. **Ibandronate** is not first-line due to limited hip fracture data.
- BMD gains are dose-dependent and greatest in the first 12 months, with prolonged maintenance after discontinuation, varying by agent.
- **Alendronate**, **risedronate**, and **intravenous (IV) zoledronic acid** are FDA-approved for postmenopausal, male, and glucocorticoid-induced osteoporosis (GIOP). Oral and IV ibandronate are approved only for postmenopausal osteoporosis. Weekly alendronate, weekly/monthly risedronate, and monthly oral and quarterly IV ibandronate produce similar BMD changes to daily regimens.
- Oral bisphosphonates require proper administration to maximize benefit and minimize GI side effects: take each tablet in the morning with ≥6 oz (180 mL) of plain water (not coffee, juice, mineral water, or milk) and at least 30 minutes before food, supplements, or medications (60 minutes for

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oral ibandronate). Delayed-release risedronate is taken immediately after breakfast with ≥4 oz (120 mL) of water. Patients should remain upright for ≥30 minutes after alendronate/risedronate and 1 hour after ibandronate to prevent esophageal irritation or ulceration.

- If a weekly dose is missed, it may be taken the next day, but two doses should not be taken on the same day. A missed monthly dose can be taken up to 7 days before the next scheduled dose.
- Common bisphosphonate adverse effects include nausea, abdominal pain, and dyspepsia. Esophageal, gastric, or duodenal irritation, ulceration, perforation, or bleeding may also occur. IV bisphosphonates commonly cause fever, flu-like symptoms, and injection-site reactions.
- Rare adverse effects include osteonecrosis of the jaw (ONJ) and subtrochanteric femoral (atypical) fractures. ONJ is more frequent in cancer patients receiving high-dose IV therapy.
- The optimal therapy duration is unknown. Some experts suggest a bisphosphonate "holiday" in postmenopausal women after 5 years of oral or 3 years of IV therapy if fracture history is minimal, hip BMD T-score is more than −2.5, and overall fracture risk is not high.
- Continuation of oral bisphosphonates for up to 10 years or IV therapy for 6 years may be considered in women who initially have very high fracture risk and remain high risk. During a drug holiday, patients should be monitored and therapy restarted if significant BMD loss or fractures occur.

TABLE 3-2

Medications Used to Prevent and Treat Osteoporosis

Drug	Brand Name	Dose	Comments
Antiresorptive Medications—Nutritional Supplements			
Calcium	Various	Adequate daily intake: IOM: 200–1200 mg/day, varies per age; supplement dose is difference between required adequate intake and dietary intake Immediate-release doses should be <500–600 mg	Recommend food first to achieve goal intake. Available in different salts including carbonate and citrate, absorption of other salts not fully quantified. Different formulations including chewable, liquid, gummy, softgel, drink, and wafer; different combination products. Review package to determine number of units to create a serving size and desired amount of elemental calcium. Give calcium carbonate with meals to improve absorption.
Vitamin D D_3 (cholecalciferol) D_2 (ergocalciferol)	Over the counter Tablets: 400, 1000, and 2000 units Capsule: 400, 1000, 2000, 5000, and 10,000 units Gummies: 300, 500, and 1000 units Drops: 300, 400, 1000, and 2000 units/mL or	Adequate daily intake: IOM: 400–800 units/day to achieve adequate intake; NOF: 800–1000 units orally daily; if low 25-hydroxyvitamin D concentrations, malabsorption, or altered metabolism, higher doses (>2000 units daily) might be required. Vitamin D deficiency: 50,000 units orally once to twice weekly for 8–12 weeks; repeat as needed until therapeutic concentrations	Read labels to determine if the vitamin D source is plant-based if desired by patient. Slight advantage of D_3 over D_2 for increasing serum 25-hydroxyvitamin D concentrations. For drops, make sure measurement is correct for desired dose. Ability of sprays, lotions, and creams to resolve deficiencies or maintain adequate intakes is unknown.

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	drop Solution: 400 and 5000 units/mL Spray: 1000 and 5000 units/spray Creams and lotions: 500 and 1000 units per ¼ teaspoonful Prescription Capsule: 50,000 units Solution: 8000 units/mL		
Antiresorptive Prescription Medications			
Bisphosphonates			
Alendronate	Fosamax Fosamax Plus D Binosto (effervescent tab)	Treatment: 10 mg orally daily or 70 mg orally weekly Prevention: 5 mg orally daily or 35 mg orally weekly	Generic available for weekly tablet product. 70 mg dose is available as a tablet, effervescent tablet, oral liquid, or combination tablet with 2800 or 5600 units of vitamin D_3. Administered in the morning on an empty stomach with 6–8 ounces of plain water. Do not eat and remain upright for at least 30 minutes following administration. Do not coadminister with any other medication or supplements, including calcium and vitamin D.
Ibandronate	Boniva	Treatment: 150 mg orally monthly, 3 mg IV quarterly Prevention: 150 mg orally monthly	Generic available for oral product. Administration instructions are the same as for alendronate, except must delay eating and remain upright for at least 60 minutes.
Risedronate	Actonel Atelvia (delayed-release)	Treatment and prevention: 5 mg orally daily, 35 mg orally weekly, 150 mg orally monthly	Generic available for immediate-release product. 35 mg dose is also available as a delayed-release product. Administration instructions are the same as for alendronate, except delayed-release product is taken immediately following breakfast.
Zoledronic acid	Reclast	Treatment: 5 mg IV infusion yearly Prevention: 5 mg IV infusion every 2 years	Generic available Can premedicate with acetaminophen to decrease infusion reactions. Contraindicated if CrCl <35 mL/min Also marketed under the brand name Zometa (4 mg) with different dosing for oncology-related indications.
RANK Ligand Inhibitor			
Denosumab	Prolia	Treatment: 60 mg SC every 6 months	Administered by a healthcare practitioner.

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			Correct hypocalcemia before administration. Also marketed under the brand name Xgeva with different dosing for oncology indications.
Estrogen Agonist/Antagonist and Tissue Selective Estrogen Complex			
Raloxifene	Evista	60 mg orally daily	Generic available.
Bazedoxifene with CEE	Duavee	20 mg plus 0.45 mg CEE orally daily	For postmenopausal females with a uterus; no progestogen needed. Bazedoxifene monotherapy available in some countries.
Calcitonin (salmon)	See comments	200 units (1 spray) intranasally daily, alternating nares every other day	Nasal formulation only available as a generic. Refrigerate nasal spray until opened for daily use, then room temperature. Prime with first use. Also available as a subcutaneous injection (Miacalcin).
Anabolic Agents			
Recombinant Human Parathyroid Hormone (PTH 1–34 Units)			
Teriparatide	Forteo	20 mcg SC daily	First dose sitting or lying. Refrigerate before and after each use. Use new needle with each dose. Inject thigh or stomach. Discard after 28 days. Biosimilars and other teriparatide products available.
Human Parathyroid Hormone–Related Peptide (PTHrP[1–34]) Analog			
Abaloparatide	Tymlos	80 mcg SC daily for up to 2 years	First dose sitting or lying. Refrigerate before use; then keep at room temperature. Use new needle with each dose. Inject in abdomen. Discard after 30 days.
Anabolic and Antiresorptive Agent			
Sclerostin inhibitor			
Romosozumab	Evenity	210 mg SC monthly for 1 year; administered as two single-use 105-mg prefilled syringes	Correct hypocalcemia before administration. Refrigerate. Leave at room temperature for at least 30 minutes before use. Provider administration, exploring patient self-administration. Inject in abdomen, thigh, or upper arm; preferably each injection at a different site.

CEE, conjugated equine estrogens; CrCl, creatinine clearance; IOM, Institute of Medicine; IV, intravenously; NOF, National Osteoporosis Foundation; SC, subcutaneously.

Denosumab

- **Denosumab** (Prolia) is a RANK ligand inhibitor that reduces osteoclast survival and function. It is FDA-approved for osteoporosis treatment in postmenopausal women and men at high fracture risk, GIOP, increasing bone mass in men on androgen-deprivation therapy for nonmetastatic prostate cancer, and in women on adjuvant aromatase inhibitors for breast cancer who are at high fracture risk.
- Over 3 years, denosumab significantly reduced vertebral, nonvertebral, and hip fractures in postmenopausal women with low bone density. Long-term treatment up to 10 years continues to increase BMD and prevent fractures.
- Denosumab is administered as a 60-mg subcutaneous (SC) injection in the upper arm, upper thigh, or abdomen every 6 months.

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- As with bisphosphonates, ONJ and atypical femoral fractures are rare. Hypocalcemia may occur, and existing hypocalcemia should be corrected before starting therapy.
- The manufacturer recommends checking serum calcium, magnesium, and phosphorus 10–14 days after denosumab in patients at risk for hypocalcemia.
- Patients with estimated glomerular filtration rate <30 mL/min/1.73 m^2 or on hemodialysis should have calcium monitored weekly for the first month, then monthly.

Mixed Estrogen Agonists/Antagonists (EAAs) and Tissue-Selective Estrogen Complexes

- **Raloxifene** (Evista) is an EAA that acts as an estrogen agonist on bone and antagonist on breast receptors, with minimal uterine effects. It is approved for prevention and treatment of postmenopausal osteoporosis and for reduction of invasive breast cancer risk in postmenopausal women with osteoporosis.
- **Bazedoxifene** is an EAA that is an agonist on bone and antagonist on uterus and breast; however, breast cancer risk reduction has not been shown. Duavee, a combination of bazedoxifene with **conjugated equine estrogens (CEE)**, is approved for preventing postmenopausal osteoporosis and treating vasomotor symptoms.
- Raloxifene and bazedoxifene reduce vertebral but not hip fractures. They increase spine and hip BMD, though less than bisphosphonates, and benefits are lost rapidly after discontinuation, with bone loss returning to pretreatment rates.
- Hot flushes are common with raloxifene but decrease with bazedoxifene/CEE. Raloxifene rarely causes endometrial thickening or bleeding, whereas bazedoxifene reduces these events, eliminating the need for progestogen when combined with CEE. Leg cramps and muscle spasms are common with both agents.
- Raloxifene carries a boxed warning for increased risk of venous thromboembolism and stroke-related death. Bazedoxifene/CEE shares all class-related estrogen adverse effects, including higher risk of thromboembolic events.

Calcitonin

- **Calcitonin** is FDA-approved for osteoporosis in women at least 5 years postmenopause. Intranasal dosing (200 units daily) reduces only vertebral fractures, and benefits fade within 1–2 years after stopping therapy. It is considered a last-line option because more effective treatments are available.
- Intranasal calcitonin may provide short-term (up to 4 weeks) pain relief for acute vertebral fractures but should not replace standard analgesics or osteoporosis treatments.

Hormone Therapies

- **Estrogen** therapy is FDA-approved for prevention, not treatment, of postmenopausal osteoporosis. It may be considered in women with early menopause who need bone protection and relief of vasomotor symptoms, while other therapies are reserved for treatment closer to average menopause age.
- Estrogen with or without progestogen significantly reduces bone loss and fracture risk. Oral and transdermal estrogens, at equivalent doses and in continuous or cyclic regimens, have similar BMD effects, which are dose-dependent, with some benefit at lower doses. Bone loss accelerates and fracture protection is lost when therapy is discontinued.
- **Testosterone** treats hypogonadism in men, but an osteoporosis medication should be added if fracture risk is high. Although fracture data are lacking, testosterone may improve BMD.

Anabolic Agents

Parathyroid Hormone Analogs

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- **Abaloparatide** (Tymlos), a parathyroid hormone–related peptide analog, and **teriparatide** (Forteo), a parathyroid hormone (PTH) analog, are indicated for postmenopausal women with osteoporosis at high fracture risk—defined by multiple risk factors, prior osteoporotic fracture, or failure/intolerance of other therapies. They are also approved to increase bone mass in high-risk men who have failed or cannot tolerate other osteoporosis treatments. Teriparatide is additionally approved for GIOP in adults.
- Intermittent daily SC teriparatide increases bone formation with a smaller rise in resorption, producing a net anabolic effect. Abaloparatide has even less stimulation of resorption, remodeling, and calcium mobilization. Abaloparatide demonstrates less of an effect on activating bone resorption and remodeling and calcium mobilization than teriparatide.
- Two years of either agent reduces vertebral and nonvertebral fracture risk in postmenopausal women. Abaloparatide increases BMD in men, though fracture data are lacking. BMD declines after discontinuation, but loss can be limited by starting an antiresorptive agent.
- Transient hypercalcemia may occur and is less frequent with abaloparatide than teriparatide (3.4% vs 6.4%). Both drugs carry a boxed warning due to osteosarcoma seen in rats, though postmarketing data show no increased risk in humans.
- Because anabolic effects diminish with prolonged use, lifetime treatment is generally limited to 2 years, with any additional teriparatide use based on risk–benefit assessment.
- PTH analogs are contraindicated in patients with hypercalcemia, metabolic bone diseases other than osteoporosis, metastatic or skeletal cancers, prior radiation therapy, or in premenopausal women of childbearing potential.

Romosozumab

- **Romosozumab** (Evenity) is a humanized monoclonal antibody that binds sclerostin, stimulating bone formation and reducing bone resorption—an effect that distinguishes it from other anabolic agents. It is FDA-approved for postmenopausal women at high fracture risk, defined by multiple risk factors, prior osteoporotic fracture, or failure/intolerance of other therapies.
- Romosozumab increases BMD at the lumbar spine, total hip, and femoral neck in postmenopausal females and in men. After 1 year of therapy in postmenopausal females, romosozumab decreased vertebral fractures and clinical fractures, with a nonsignificant decrease in nonvertebral fractures. However, nonvertebral fractures and hip fractures were decreased after 1 year of romosozumab followed by 1 year of alendronate. Denosumab use following 1 year of romosozumab therapy also maintains gains in BMD and reduction in fracture risk. To prevent BMD loss after discontinuation, 1 year of denosumab or alendronate after romosozumab maintains and further increases BMD at both sites.
- Common adverse effects include headache, arthralgia, and mild injection-site reactions. Romosozumab may also cause hypocalcemia, so serum calcium should be corrected before treatment. Myocardial infarction, stroke, and cardiovascular death are included in its boxed warning. Romosozumab should not be used within 1 year of myocardial infarction or stroke, and its benefits and risks must be carefully evaluated in patients with or at risk for cardiovascular disease. Rare cases of ONJ and atypical femoral fractures have been reported.
- Therapy should be limited to 1 year (12 monthly doses) due to waning effectiveness with longer use.

Sequential and Combination Therapy

- In sequential therapy, an anabolic agent is given first—1 year of romosozumab or 2 years of teriparatide or abaloparatide—to increase bone remodeling units and bone mass. This is followed by an antiresorptive agent to preserve BMD gains and maintain fracture protection. Because of the high cost of anabolic therapy, this approach is generally reserved for patients with severe osteoporosis.

  ✓ Starting with an anabolic agent followed by an antiresorptive is preferred, as beginning with an antiresorptive has a smaller impact on BMD. Patients who fracture or continue losing bone mass on antiresorptive therapy may reasonably be switched to an anabolic agent.

  ✓ Switching from an oral bisphosphonate to denosumab can produce small BMD gains. This approach may be used during a bisphosphonate drug holiday or for treatment failures (ie, no BMD improvement or fractures).

- Combination therapy with multiple osteoporosis medications is not indicated because it provides no proven fracture benefit, increases cost, may

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overly suppress bone turnover, and can raise adverse effects. It may be reasonable to add a more potent osteoporosis medication to hormone therapy for menopausal symptom management. When raloxifene is used for breast cancer prevention, another antiresorptive may be added if hip fracture risk is high.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

- Glucocorticoids reduce bone formation by decreasing osteoblast proliferation and differentiation and increasing their apoptosis. They also raise osteoclast numbers and bone resorption, lower calcium absorption, and increase renal calcium excretion.
- All glucocorticoid doses and formulations can increase bone loss and fracture risk. Even oral prednisone doses of 2.5–7.5 mg daily (or equivalent) for over 3 months raise fracture risk, which further increases with chronic use or intermittent high-dose therapy. The risk is also greater with oral therapy compared to inhaled or intranasal therapy.
- The greatest bone loss occurs during the first 3–6 months of glucocorticoid therapy, with fracture risk rising within 3 months and peaking at 1 year.
- Adults ≥40 should have an initial BMD assessment as soon as possible after starting glucocorticoids. Adults under 40 may also undergo BMD with vertebral fracture assessment, though FRAX is not used. Repeat BMD testing is recommended every 1–2 years while on glucocorticoids or osteoporosis treatment.
- All patients using glucocorticoids should follow a bone-healthy lifestyle and consume 1000–1200 mg elemental calcium and 600–800 IU vitamin D daily to maintain therapeutic 25-hydroxyvitamin D levels. Use the lowest effective corticosteroid dose and duration.
- Prescription medication recommendations are based on fracture risk and age. Alendronate, risedronate, zoledronic acid, denosumab, and teriparatide are FDA-approved for GIOP.
- In GIOP, teriparatide increases BMD and reduces fractures more effectively than oral bisphosphonates. Because glucocorticoids suppress bone formation, anabolic agents are preferred for patients at higher risk.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess medication adherence and tolerability at each visit.
- Monitoring fractures, back pain, and height loss can help detect worsening osteoporosis.
- Obtain a central DXA every 1–2 years after medication initiation until BMD is stable, at which time the interval for reassessment can be lengthened. More frequent monitoring may be warranted in patients with conditions associated with high rates of bone loss (eg, glucocorticoid use).
- Bone turnover markers can help detect nonadherence or treatment failure, but they are not routinely used due to high variability and lack of consensus on interpretation.

See Chapter 117, Osteoporosis, authored by Jill S. Borchert, Erin M. Slazak, and Joseph P. Fava for a more detailed discussion of this topic.

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